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Date: May 20, 2002

To: Examiner Anne Marie Baker
U.S. Patent and Trademark Office

Facsimile No: 703-308-4242

From: Anthony Kuhlmann, Ph.D.

Re: U.S. Application No: 09/478,099
Attorney Docket No: 50069/002002

Pages: 3A, including this one

Message: Dear Examiner Baker:

Attached as requested is Exhibit A which was originally filed on February 14, 2002.

Please note that we no longer handle this case. It has been transferred to the following attorney listed below.

Ronald I. Eisenstein, Esq.
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If you need anything further, please let me know.

Anti-VEGF Therapy for Subfoveal Choroidal Neovascularization Secondary to Age-related Macular Degeneration: Phase 1B Study Results

The Eyetech Study Group[1]

[1]See page 25 for list of authors and financial/management disclosures

Presented at the American Academy of Ophthalmology Meeting, New Orleans, LA, November 2001

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PRÉCIS:

A Phase 1B clinical trial of the anti-VEGF aptamer with and without photodynamic therapy in patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration revealed an excellent safety profile and justification for further clinical study.

STRUCTURED ABSTRACT:

Purpose: There is evidence to suggest that anti-VEGF therapy may be useful to treat ocular neovascularization. A Phase 1A single intravitreal injection study of anti-VEGF therapy for patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) revealed an excellent safety profile. We performed a Phase 1B multiple injection study of anti-VEGF therapy with or without photodynamic therapy for patients with subfoveal CNV secondary to AMD to determine the safety profile of multiple injection therapy.

Design & Methods: A Phase 1B multiple dose study of intravitreal injection of the drug with or without photodynamic therapy was performed in 21 patients with subfoveal CNV secondary to AMD.

Results: No significant safety issues related to the drug were revealed. Ophthalmic evaluation revealed that 87.5% of patients that received the anti-VEGF aptamer alone showed stable or improved vision 3 months after treatment and that 25% of eyes demonstrated a 3-line or greater improvement in vision on the ETDRS chart at this time period. A 60% 3-line gain at 3 months was noted in patients that received both the anti-VEGF aptamer and photodynamic therapy.

Conclusion: Anti-VEGF therapy is a promising treatment for various forms of ocular neovascularization, including AMD and diabetic retinopathy. Multiple intravitreal injections of the anti-VEGF aptamer were well tolerated in this Phase 1B study. Further clinical trials are necessary to demonstrate the efficacy and long-term safety of anti-VEGF therapy for AMD.

INTRODUCTION:

Choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) is a leading cause of blindness in the elderly[1-2]. Thermal laser photocoagulation and photodynamic therapy (PDT) have been shown to be beneficial for subgroups of such patients[3-6]. However, only a fraction of eyes meet the eligibility criteria for such therapeutic interventions and those treated have a high recurrence rate.

Recent pre-clinical studies have suggested that pharmacological intervention or anti-angiogenesis therapy may be useful to treat various forms of ocular neovascularization, such as CNV. Much of this work has focused on blocking vascular endothelial growth factor (VEGF)[7-12], which has demonstrated potential importance in the pathogenesis of both CNV secondary to AMD and diabetic retinopathy. Studies have shown regression or prevention of neovascularization in multiple vascular beds (iris[13], retina[14-15], choroid[16]) in several animal models (primate[13,16], mouse[15], and rat[14]) using various types of anti-VEGF agents (including aptamers[14] and antibody fragments[16]).

In addition to a potential anti-angiogenic effect, anti-VEGF therapy may be useful as an anti-permeability agent[9]. VEGF was initially coined vascular permeability factor due to its potent ability to induce leakage from blood vessels. Recent laboratory work suggests that anti-VEGF therapy may inhibit diabetes-induced blood-retinal barrier breakdown in animals[17].

Anti-VEGF therapy may, therefore, represent a two-prong attack on CNV via its anti-angiogenic and anti-permeability properties.

We have previously reported on a Phase 1A safety study of a single intravitreal injection of the anti-VEGF aptamer in patients with subfoveal CNV secondary to AMD[14]. In this study 80% of eyes showed stable or improved vision and 26.7% of eyes that completed a 3-month regimen had a 3-line improvement of vision on the ETDRS chart. No significant related adverse events were reported locally or systemically.

We report the results of a Phase 1B safety study using multiple intravitreal injections of the anti-VEGF aptamer in patients with subfoveal CNV secondary to AMD with or without PDT.

PATIENTS AND METHODS:

STUDY DESIGN

A multi-center, open-label, repeat dose Phase IB study of 3mg/eye of EYE001 (anti-VEGF aptamer) was performed in patients with subfoveal CNV secondary to AMD with a visual acuity worse than 20/100 in the study eye and better or equal to 20/400 in the fellow eye. If 3 or more patients experienced Dose-Limiting Toxicity (DLT's), the dose was reduced to 2mg and then 1mg, if necessary. The intended number of patients to be treated was 20; 10 patients with the anti-VEGF aptamer alone and 10 patients with both anti-VEGF therapy and PDT. Eleven sites in the U.S. were selected for the studies.

DEFINITION OF DLT(S)

Ophthalmic DLT

Photographic Evaluation

- Accelerated formation of cataract: progression of one unit defined by the Age-Related Eye Disease Study (AREDS) Lens Opacity Grading Protocol as adapted from the Wisconsin Cataract Grading System.

Clinical Examination

- Clinically significant inflammation, which is severe (obscuring visualization of the retinal vasculature) and vision threatening.
- Other ocular abnormalities not usually seen in patients with AMD, such as retinal, arterial, or venous occlusion, acute retinal detachment, and diffuse retinal hemorrhage.
- Visual acuity: doubling or worsening of the visual angle (loss of ≥15 letters); transition to no light perception (NLP) for patients whose beginning visual acuity score is less than 15 letters unless the loss of vision is due to a vitreous hemorrhage related to the injection procedure between Days 2 through 7, Days 30-35, or Days 58-63.
- Tonometry: increase from baseline of intraocular pressure (IOP) by ≥25mmHg on two separate examinations at least one day apart or a sustained pressure of 30mmHg for more than a week despite pharmacological intervention.

Fluorescein Angiogram

Significant retinal or choroidal vascular abnormalities not seen at baseline, such as:

- Choroidal nonperfusion (effecting one or more quadrants)
- Delay in arterio-venous transit times (greater than 15 seconds)
- Retinal arterial or venous occlusion (any deviation from baseline)
- Diffuse retinal permeability alteration effecting retinal circulation in the absence of intraocular inflammation

Systemic DLT

Grade III (severe) or IV (life-threatening) toxicities, or any significant severe toxicity deemed related to study drug by the investigator.

INCLUSION CRITERIA

The ophthalmic criteria included best corrected visual acuity in the study eye worse than 20/100 on the ETDRS chart, best corrected visual acuity in the fellow eye equal to or better than 20/400, subfoveal choroidal neovascularization **with active CNV** (either classic and/or occult) of less than 12 total disc areas in size secondary to age related macular degeneration, clear ocular media and adequate pupillary dilatation to permit good quality stereoscopic fundus photography, and intraocular pressure of 21mmHg or less.

General criteria included patients of either sex, aged ≥50 years; performance Status ≤2 according to the Eastern Cooperative Oncology Group (ECOG) / World Health Organization (WHO) scale,

normal electrocardiogram (ECG) or clinically non-significant changes; women must be using an effective contraceptive, be post-menopausal for at least 12 months prior to study entry, or surgically sterile; if not, a serum pregnancy test must be performed within 48 hours prior to treatment and the result made available prior to treatment initiation, an effective form of contraceptive should be implemented for at least 28 days following the last dose of EYE001; adequate hematological function: hemoglobin ≥10 g/dl; platelet count ≥150 x 10^9/l; WBC ≥4 x 10^9/l; PTT within normal range of institution; adequate renal function: serum creatinine and BUN within 2 x the upper limit of normal (ULN) institution; adequate liver function: serum bilirubin ≤1.5 mg/dl; SGOT/ALT, SGPT/AST, and alkaline phosphatase within 2 x ULN of institution; written informed consent; and ability to return for all study visits.

EXCLUSION CRITERIA

Patients were not eligible for the study if any of the following criteria were present in the study eye or systemically: patients scheduled to receive, or have received any prior Photodynamic Therapy with Visudyne; significant media opacities, including cataract, which might interfere with visual acuity, assessment of toxicity or fundus photography; presence of other causes of choroidal neovascularization, including pathologic myopia (spherical equivalent of -8 diopters or more negative), the ocular histoplasmosis syndrome, angioid streaks, choroidal rupture and multifocal choroiditis; patients in whom additional laser treatment for choroidal neovascularization might be indicated or considered; any intraocular surgery within 3 months of study entry; previous vitrectomy; previous or concomitant therapy with another investigational agent to treat AMD except multivitamins and trace minerals; previous radiation to the fellow eye

with photons or protons; known allergies to the fluorescein dye used in angiography or to the components of EYE001 formulation; any of the following underlying systemic diseases including: uncontrolled diabetes mellitus or presence of diabetic retinopathy, cardiac disease: myocardial infarction within 12 months prior to study entry, and/or coronary disease associated with clinical symptoms, and/or indications of ischemia noted on ECG, impaired renal or hepatic function, stroke (within 12 months of study entry), active infection, active bleeding disorders, any major surgical procedure within one month of study entry, active peptic ulcer disease with bleeding within 6 months of study entry; concomitant systemic therapy with corticosteroids (e.g. oral prednisone), or other anti-angiogenic drugs (e.g. thalidomide); previous radiation to the head and neck; any treatment with an investigational agent in the past 60 days for any condition; any diagnosis of cancer in the past 5 years, with the exception of basal or squamous cell carcinoma.

STUDY MEDICATION

DRUG SUPPLY

EYE001 drug substance is a pegylated anti-VEGF aptamer. It is formulated in phosphate buffered saline at pH 5-7. Sodium hydroxide or hydrochloric acid may be added for pH adjustment.

EYE001 is formulated at three different concentrations: 3mg/100ul, 2mg/100ul and 1mg/100ul packaged in a sterile 1ml, USP Type I graduated glass syringe fitted with a sterile 27-gauge needle. The drug product is preservative-free and intended for single use by intravitreous injection only. The product should not be used if cloudy or particles are present.

The active ingredient is EYE001 Drug Substance, (Pegylated) anti-VEGF aptamer, and 30 mg/ml, 20mg/ml and 10mg/ml concentrations. The excipients are Sodium Chloride, USP; Sodium Phosphate Monobasic, Monohydrate, USP; Sodium Phosphate Dibasic, Heptahydrate, USP; Sodium Hydroxide, USP; Hydrochloric acid, USP; and Water for injection, USP.

DOSE AND ADMINISTRATION

Preparation

The drug product is a ready-to-use sterile solution provided in a single-use glass syringe. The syringe was removed from refrigerated storage at least 30 minutes (but not longer than 4 hours) prior to use to allow the solution to reach room temperature. Administration of the syringe contents involved attaching the threaded plastic plunger rod to the rubber stopper inside the barrel of the syringe. The rubber end cap was then removed to allow administration of the product.

Treatment Regimen and Duration

EYE001 was administered as a 100µl intravitreal injections on three occasions at 28 day intervals. Patients were enrolled to receive 3mg/injection. If 3 or more patients experienced Dose-Limiting Toxicity (DLT's), the dose was reduced to 2mg and further to1mg, if necessary, each in an additional 10 patients.

PDT ADMINISTRATION

PDT was given with EYE001 only in cases with predominantly classic CNV. The standard requirements and procedures for PDT administration were used[6]. PDT was required to be given 5-10 days prior to administration of the anti-VEGF aptamer.

STUDY CONDUCT

PATIENT ENROLLMENT

Before recruitment of patients into the study, written Institutional Review Board (IRB) approval of the protocol, and informed consent form were obtained. Case report form screening pages were completed by study site personnel. Patients who meet the eligibility criteria and have provided written informed consent were enrolled in the study.

FOLLOW-UP SCHEDULE:

Patients were clinically evaluated by the ophthalmologist several days after injection and again one-month later just prior to the next injection. ETDRS visual acuities, Kodachrome photography and fluorescein angiography were performed monthly for the first 4 months.

ENDPOINTS:

The safety parameters given under the DLT section above were the primary endpoint of the studies. In addition, the percentage of patients with stabilized (0 line change or better) or improved vision at 3 months, the percentage of patients with a 3-line or greater improvement at 3 months, and the need for PDT re-treatment at 3 month as determined by the investigator were other endpoints studied.

RESULTS:

No serious related adverse events were noted for the 21 patients treated in this study. Three patients experienced serious unrelated adverse events. One patient, an 86 year-old woman with a long-standing history of peripheral vascular disease as well as borderline hypertension and type II diabetes mellitus experienced 2 myocardial infarctions, the second of which was fatal. The first event occurred 11 days following the first intraocular injection of anti-VEGF aptamer. The second event occurred 16 days following the third and last injection. The acute myocardial infarctions took place approximately 2 months apart. These events were believed to be unrelated to aptamer therapy by the investigator and systemic levels of the drug are negligible based on pharmacokinetic data. A second patient, a 76 year-old man with a 10-month history of depression attempted suicide with ingestion of acetaminophen 11 days after the third and last dose of anti-VEGF aptamer. The patient's mental condition improved. Treatment of the patient has remained unchanged and the patient is presently followed in the study. A third patient, a 74 year-old man with a past medical history significant for 14-month history of supraventricular

tachycardia and a one month history of sick sinus syndrome experienced palpitations requiring hospitalization two days following the first dose of anti-VEGF aptamer. The patient was cardioverted successfully and discharged from the hospital on the following day. Twelve days following discharge, the patient again experienced palpitations and was diagnosed with atrial fibrillation and supraventricular tachycardia. Cardioversion was attempted pharmacologically without success. The patient was then electrically cardioverted which restored normal sinus rhythm. A dual-chamber pacemaker was placed and the patient was maintained on propafenone and digoxin. Treatment of the patient has remained unchanged and the patient is presently followed in the study.**able 1** shows the unrelated or non-severe events reported in these groups. In patients treated with the anti-VEGF aptamer alone, ocular adverse events probably associated with administration of the anti-VEGF aptamer included vitreous floaters (4 Events), mild anterior chamber inflammation (3 Events), ocular irritation (2 Events), increased intraocular pressure (1 Event), intraocular air (1 Event), vitreous haze (1 Event), subconjunctival hemorrhage (1 Event), eye pain (1 Event), lid edema/erythema (1 Event), dry eye (1 Event) and conjunctival injection (1 Event). Events possibly related to administration of anti-VEGF aptamer included, asteroid hyalosis (1 Event), abnormal vision (1 Event) and fatigue (1 Event). Events termed unrelated to administration of anti-VEGF aptamer included headache (1 Event) and weakness (1 Event). In patients treated with the anti-VEGF aptamer and PDT adverse events probably associated with this combination of therapy included ptosis (5 Events), mild anterior chamber inflammation (4 Events), corneal abrasion (3 Events), eye pain (3 Events), foreign body sensation (2 Events), chemosis (1 Event), subconjunctival hemorrhage (1 Event) and vitreous prolapse (1 Event). Events possibly related to combination therapy included fatigue (2 Events). Events unrelated to combination therapy included pigment epithelial detachment (1

Event), joint pain (1 Event), upper respiratory infection (1 Event) and bladder infection (1 Event). The increase in ptosis and corneal abrasion seen in the setting of combination therapy may be related to the use of a contact lens in association with PDT. Of note, all instances of anterior chamber inflammation or vitreous haze were mild and transient in nature.

Two patients elected to prematurely terminate their participation in the study. One patient believed that her vision was not improving and did not want further injections. The other patient had depression and transportation problems. Both patients withdrew their consent prior to the third and last injection of the aptamer. Visual acuity in both patients remained stable throughout their participation in the study. A third patient died prior to the final visit.

No dose decrease was required for any patients in the study. Review of color photographs and fluorescein angiograms of these patients revealed no signs of retinal vascular or choroidal toxicity.

Of those patients (N=8) who completed the 3-month treatment regimen of the anti-VEGF aptamer alone 87.5% had stabilized or improved vision and 25.0% had a 3-line improvement of vision on the ETDRS chart at 3 months **(Table 2 & Figures 1 & 2).**

Eleven patients were treated with both the anti-VEGF aptamer and PDT. In this group of patients (N=10) who completed the 3-month treatment regimen, 90% had stabilized or improved vision and 60% showed a 3-line improvement of vision on the ETDRS chart at 3 months **(Table**

3 & Figures 3 & 4). These 3-line improvements included gains of +3, +5, +4, +4, +6, and +3 ETDRS lines of vision.

Of the remaining patients who did not show a 3-line gain, only one showed a loss of vision at 3 months and this patient lost only one line of vision at this time point. No patient in this group lost more than one line of vision at 3 months.

Repeat PDT treatment at 3 months (whose need was solely determined by the investigator) was performed in 4 of 10 eyes (40%) that participated for the complete duration of the study.

DISCUSSION:

Angiogenesis, or abnormal blood vessel growth has been implicated as an important cause of pathological states in many areas of medicine including ophthalmology, cancer, and rheumatology. Vascular endothelial growth factor (VEGF) appears to be critical in the development of ocular neovascularization[18-20] and, thus, anti-VEGF therapy is promising as a new therapy for AMD and diabetic retinopathy.

Studies in humans have shown that high concentrations of VEGF are present in the vitreous in angiogenic retinal disorders but not in inactive or non-neovascularization disease states[19-20]. Excised human CNV after experimental submacular surgery have also shown elevated VEGF levels[18].

Animal studies have shown that injection of VEGF into the vitreous can cause a diabetic retinopathy-like state[21]. In addition, VEGF has shown powerful inhibitory effects on both angiogenesis and permeability in various animal models of ocular neovascularization. For example, in the mouse model of retinopathy of prematurity, the anti-VEGF aptamer (Eyetech) showed 80% inhibition of retinal neovascularization compared to controls[14]. In the monkey model of laser-induced CNV, the incidence of CNV (defined angiographically) was significantly lower in prevention eyes (eyes treated with a recombinant anti-VEGF antibody fragment from Genentech) than in Control eyes ($p<0.001$)[16]. Subsequent treatments in this model were associated with less leakage in eyes with established CNV.

Recently, pre-clinical work has shown that VEGF may be important in causing vessel leakage in diabetic retinopathy and that the diabetes-induced blood-retinal barrier breakdown can be dose-dependently inhibited with anti-VEGF therapy (in this experiment using VEGF $TrapA_{40}$ – a highly specific VEGF-neutralizing soluble Flt/Fc construct from Regeneron)[17]. These studies highlight the potential anti-angiogenic and/or anti-permeability properties of anti-VEGF therapy.

The results of this Phase 1B multiple intravitreal injection clinical study of anti-VEGF therapy expand the excellent safety profile reported by our Phase 1A single-injection study. Specifically, the Phase 1B study shows the intraocular and systemic safety of three consecutive anti-VEGF aptamer intravitreal injections given monthly. No serious related adverse events were noted. The adverse events encountered appeared to be unrelated or minor events in some cases probably due to the intravitreal injection itself. Further study is necessary and underway to determine the long-term safety profile of the anti-VEGF aptamer.

No definitive conclusions regarding efficacy can be deduced from this study due to the lack of controls, small sample size, and limited follow-up period. Nevertheless, the 3-line gain observed in 25% of the aptamer only treated group at 3 months compares favorably to historical controls such as the results of the pivotal trial of PDT (2.2%) and its controls (1.4%) at 3 months[6] and a sham radiation control group (3%)[22] where no more than 3% of patients showed such an improvement at this same time period.

The 25% 3-line gain at 3 months is consistent with the 26.7% improvement rate noted in the Phase 1A study of the aptamer. It may be that the anti-permeability effects of the drug caused resorption of subretinal fluid and, thus improved vision in these cases. Interestingly, a recent study using an anti-VEGF antibody fragment from Genentech also showed a 26% 3-line gain rate in a Phase 1 clinical trial[23]. This antibody fragment shares the same mechanism of blocking extracellular VEGF as the anti-VEGF aptamer.

The stabilization or improvement rate of 87.5% observed at 3 months in this study also compares favorably with the 50.5% rate for the PDT-treated patients in that pivotal trial[6], the 44% rate in the PDT controls[6], and 48% rate in the sham radiation control group[22].

The 60% 3-line gain at 3 months in the patients that received both the anti-VEGF aptamer and PDT was also very encouraging. In the pivotal Phase 3 PDT trial only 2.2% of patients showed such visual improvement[6]. Both of these study groups included eyes with classic subfoveal CNV. The improvement in vision observed in these eyes is supported by the finding that the

investigators choose to re-treat with PDT at 3 months in only 40% of cases compared to the 93% re-treatment rate reported in the pivotal PDT trial[6].

This study confirms the short-term safety of intravitreal injections of the anti-VEGF aptamer in patients with subfoveal CNV. Future studies must address the long-term safety of such therapy. We strongly emphasize that no conclusions concerning efficacy can be made from the data in this small non-controlled limited Phase 1 safety study. Only a prospective randomized controlled clinical trial can determine if anti-VEGF therapy is beneficial and safe for patients with CNV – such a Phase 2/3 pivotal trial is presently underway to evaluate this potential treatment in approximately 1,000 patients in over 100 centers worldwide.

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FINANCIAL DISCLOSURE:

Drs. Adamis, Blumenkrantz, Goldberg, Gragoudas, Guyer, Miller, O'Shaughnessy, Patel, and Yannuzzi all have a financial interest and/or managerial position in Eyetech Pharmaceuticals, Inc.

Table 1A.

ADVERSE EVENTS ASSOCIATED WITH ADMINISTRATION OF ANTI-VEGF APTAMER ALONE OR IN COMBINATION WITH PDT

Adverse Event	Anti-VEGF Aptamer N (%) 10 Patients		Anti-VEGF Aptamer & PDT N (%) 11 Patients	
Ptosis	0		5 (45.4)	
Lid Edema/Erythema	1 (10)		2 (18.2)	
Conjunctival Injection	1 (10)		0	
Chemosis	0		1 (9.1)	
Subconjunctival Hemorrhage	1(10)		1 (9.1)	
Dry Eye	1 (10)		0	
Corneal Abrasion	0		3 (27.3)	
Anterior Chamber Inflammation	3 (30)	1+ Cells	4 (36.4)	Trace Cells
		Trace Cells		1+ KP; Trace Cells
		Trace Cells		Trace Cells
				Trace Cells
IOP Increase	1 (10)		0	
Pupillary Abnormalities	0		0	
Rubeosis	0		1 (9.1)	
Cataract	0		0	
Vitreous Haze	1 (10)		2 (18.2)	
Vitreous Prolapse	0		1 (9.1)	
Vitreous Floaters	4 (40)		0	
Asteroid Hyalosis	1 (10)		0	
Intraocular Air	1 (10)		0	
Peripapillary Hemorrhage	0		1 (9.1)	
Pigment Epithelial Detachment	0		1 (9.1)	
Abnormal Vision	1 (10)		0	
Photopsia	1 (10)		0	
Foreign Body Sensation	1 (10)		2 (18.2)	
Eye Pain	1 (10)		3 (27.3)	
Blepharospasm	0		1 (9.1)	
Ocular Irritation	2 (20)		1 (9.1)	
Ocular Tenderness	0		1 (9.1)	
Ocular Pruritis	1 (10)		0	
Tearing	1 (10)		0	
Headache	1 (10)		0	
Rhinorrhea	0		1 (9.1)	
Fatigue	1 (10)		2 (18.2)	
Weakness	1 (10)		0	
Joint Pain	0		1 (9.1)	
Upper Respiratory Infection	0		1 (9.1)	
Bladder Infection	0		1 (9.1)	

Table 1B.

ADVERSE EVENTS ASSOCIATED WITH ADMINISTRATION OF THE ANTI-VEGF APTAMER ALONE

Adverse Event Relationship	Anti-VEGF Aptamer N 10 Patients
Probably:	
Vitreous Floaters	4
Anterior Chamber Inflammation	3
Ocular Irritation	2
Vitreous Haze	1
Increased Intraocular Pressure	1
Intraocular Air	1
Subconjunctival Hemorrhage	1
Conjunctival Injection	1
Eye Pain	1
Lid Edema/Erythema	1
Dry Eye	1
Possibly:	
Asteroid Hyalosis	1
Abnormal Vision	1
Fatigue	1
Unrelated:	
Headache	1
Weakness	1

Table 1C.

ADVERSE EVENTS ASSOCIATED WITH ADMINISTRATION OF THE ANTI-VEGF APTAMER & PDT

Adverse Event Relationship	Anti-VEGF Aptamer & PDT N 11 Patients
Probably:	
Ptosis	5
Anterior Chamber Inflammation	4
Corneal Abrasion	3
Eye Pain	3
Foreign Body Sensation	2
Chemosis	1
Subconjunctival Hemorrhage	1
Vitreous Prolapse	1
Possibly:	
Fatigue	2
Unrelated:	
Pigment Epithelial Detachment	1
Joint Pain	1
Upper Respiratory Infection	1
Bladder Infection	1

Table 2.

VISUAL DATA OF PATIENTS WITH SUBFOVEAL CNV TREATED WITH THE ANTI-VEGF APTAMER ALONE

Patient #	Baseline	Day 8	Day 29	Day 57	Day 85	+/- No of lines At Day 85
03-001	20/50	20/40	20/40	20/32	20/32	+2
04-001	20/125	20/64	20/80	20/80	20/80	+2
06-001	20/160	20/125	20/100	20/125	OUT	+1
07-001	20/100	20/100	20/64	20/80	20/80	+1
07-002	20/320	20/80	20/64	20/64	20/50	+8
08-001	20/125	20/125	20/100	20/100	20/160	-1
09-001	20/500	20/200	20/400	20/320 (Day 36)	OUT	+2
10-001	20/500	20/640	20/500	20/400	20/500	0
10-002	20/200	20/125	20/160	20/160	20/160	+1
10-003	20/400	20/160	20/160	20/160	20/126	+5

CHANGE IN VISION AT 3 MONTHS

	Stabilized or Improved	≥ 3 Line Improvement
EYE001 Treated - (N=8) which represents all eyes that completed the protocol.	**87.5%**	**25.0%**

Table 3.

VISUAL DATA OF PATIENTS WITH SUBFOVEAL CNV TREATED WITH THE ANTI-VEGF APTAMER COMBINED WITH PDT

Patient #	Baseline	Day 8	Day 29	Day 57	Day 85	Repeat PDT	+- No of Lines At latest time-point
06-011	20/400	20/320	20/100	20/640	20/200	NO	+3
06-012	20/250	20/160	20/125	20/125	20/80	NO	+5
08-011	20/40	20/32	20/20	20/20	20/26	YES	+2
10-011	20/160	20/160	20/160	20/160	OUT	NO	0
05-011	20/100	20/64	20/64	20/64	20/40	NO	+4
12-011	20/160	20/100	20/250	20/200	20/200	NO	-1
06-013	20/800	20/640	20/800	20/800	20/320	YES	+4
02-011	20/500	20/200	20/160	20/80	20/126	YES	+6
06-014	20/100	20/80	20/80	20/80	20/100	NO	0
06-015	20/125	20/40	20/64	20/50	20/80	NO	+2
02-012	20/500	20/500	20/125	20/320	20/250	YES	+3

	CHANGE IN VISION AT 3 MONTHS	
	Stabilized or Improved	≥3 Line Improvement
EYE001 Treated - (N=10) which represents all eyes that completed the protocol.	**90%**	**60%**

FIGURE LEGENDS:

Figure 1. (Case Report 1)

This patient with CNV presented with a cuff of subretinal fluid and blood **(A)**. The fluorescein angiogram revealed classic subfovcal CNV **(B)**. One month after intravitreal injection of the anti-VEGF aptamer the clinical exudation markedly decreased **(C)** and the angiogram showed regression of the CNV by approximately 20% **(D)**. After 2 months unexposed to drug the CNV dramatically increased in size by approximately 120% **(E)**.

Figure 2. (Case Report 2)

This patient presented with classic subfovcal CNV **(A)**. One month after an intravitreal injection of the anti-VEGF aptamer regression of the CNV is noted by approximately 30% **(B)**.

Figure 3. (Case Report 3)

This patient with subfoveal CNV **(A)** was treated with both photodynamic therapy (PDT) and three monthly injections of the anti-VEGF aptamer. The patient's vision improved by 5 ETDRS lines (20/250 to 20/80) with markedly decreased exudation clinically several months after initiating therapy **(B)**. Repeat PDT was not performed at 3 months per the decision of the investigator.

Figure 4. (Case Rep rt 4)

This patient presented with subfoveal CNV and marked peripheral hyperpermeability **(A)**, which was greatly decreased **(B)** after three monthly injections of the anti-VEGF aptamer and one treatment with photodynamic therapy.